Infection outcomes in patients with common variable immunodeficiency disorders: Relationship to immunoglobulin therapy over 22 years

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Background: Common variable immunodeficiency disorders (CVIDs) are the most common forms of symptomatic primary antibody failure in adults and children. Replacement immunoglobulin is the standard treatment, although there are few consistent data on optimal dosages and target trough IgG levels required for infection prevention.

Objective: To provide data to support the hypothesis that each patient requires an individual dose of therapeutic immunoglobulin to prevent breakthrough infections and that efficacious trough IgG levels vary between patients.

Methods: Data, collected prospectively from a cohort of 90 patients with confirmed CVIDs from 1 center over a follow-up period of 22 years, was validated and analyzed. Immunoglobulin doses had been adjusted in accordance with infections rather than to achieve a particular trough IgG level. Doses to achieve infection-free periods were determined and resultant trough levels analyzed. A smaller group of patients with X-linked agammaglobulinemia was analyzed for comparison.

Results: Patients with a CVID had a range of trough IgG levels that prevented breakthrough bacterial infections (5-17 g/L); viral and fungal infections were rare. Doses of replacement immunoglobulin to prevent breakthrough infections ranged from 0.2 to 1.2 g/kg/mo. Those with proven bronchiectasis or particular clinical phenotypes required higher replacement doses. Patients with X-linked agammaglobulinemia showed a similar range of IgG levels to stay infection-free (8-13 g/L).

Conclusion: These data offer guidance regarding optimal doses and target trough IgG levels in individual patients with CVIDs with or without bronchiectasis and for particular clinical phenotypes. The goal of replacement therapy should be to improve clinical outcome and not to reach a particular IgG trough level. (J Allergy Clin Immunol 2010;125:1354-60.)

Key words: *Long-term follow up, infection outcome, complications, CVIDs, clinical phenotypes*

Common variable immunodeficiency disorders (CVIDs) form the most common symptomatic primary antibody failure in adults and children. Diagnosis relies on low serum immunoglobulin levels, inability to respond to test immunizations, and exclusion of other known causes of immunodeficiency.[1] Replacement immunoglobulin is the standard treatment for patients with CVIDs, with intravenous and subcutaneous routes replacing the painful and less effective intramuscular route.[2] Despite the ability to administer larger doses by the intravenous and subcutaneous routes, some patients remain susceptible to acute breakthrough and chronic infections as well as a myriad of noninfectious complications.[3]

The efficacy of replacement therapy was evidenced by studies of infection prevention that resulted in raising serum trough IgG levels and reducing rates of severe and moderate infections.[4-13] It has also been suggested that each patient requires an individual immunoglobulin dose to maintain an individual target IgG level to prevent breakthrough infections.[14-17] However, there are no data to support this other than in 2 illustrative patients.[15] Consequently, there is some confusion over defining optimal dosages and target trough IgG levels for patients.

There have been studies and clinical trials into the frequency and severity of infections in relation to trough IgG levels and dose of replacement therapy, but these have had mixed results because of the relatively small numbers of patients involved. Most studies report a significant decrease in infection rates with increased doses of immunoglobulin and a coinciding increase in trough IgG levels.[9,13,16-20] In contrast, some report no change in infection frequency[21-24] and no correlation with serum IgG levels.[25] However, patient numbers are low (a maximum of 27 patients with CVIDs), and reports often include several types of antibody deficiency and are limited by short follow-up periods[20] and little infection detail, comparing only short periods before and after immunoglobulin replacement therapy.[11,12] Most published guidelines recommend trough IgG levels of around 6 to 8 g/L to be achieved with a dose of 400 mg/kg every 3 to 4 weeks[26-29]; consensus is based largely on expert opinion and systematic reviews of such limited data.

Patients with CVIDs are more susceptible to a range of complications including autoimmune, polyclonal lymphoproliferative, gastrointestinal, and malignant complications, as well as infections. The recent study of 334 patients with confirmed CVIDs provided further subgrouping of these diseases by the presence or absence of disease-related complications. Five distinct clinical phenotypes were proposed: those of no complications, autoimmunity, polyclonal lymphoproliferation, enteropathy, and lymphoid malignancy.[3]

We had the opportunity to analyze validated data from a large cohort of 90 clinically phenotyped patients with CVIDs in

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Abbreviations used
CVID: Common variable immunodeficiency disorder
LIP: Lymphoid interstitial pneumonitis
pR^2: Partial regression coefficient
XLA: X-linked agammaglobulinemia

1 center, collected prospectively over 22 years. Our local management policy has been to adjust immunoglobulin doses in real time in accordance with infection episodes rather than to achieve a particular trough IgG level. Initial doses of 0.4 g/kg/mo IgG are used for patients without chronic lung disease and 0.6 g/kg/mo for those with bronchiectasis.[26-29] Doses are adjusted in line with breakthrough infections. In the absence of serious breakthrough infections, a rate of 3 moderate bacterial infections per year justifies an increase in immunoglobulin dosage of around 0.15 g/kg/mo, usually given as weekly subcutaneous immunoglobulin or intravenous immunoglobulin every 2 weeks.

We examine the relationships among therapeutic immunoglobulin dose, trough serum IgG levels, and infection rates. The objective was to provide data to support the hypothesis that each patient requires an individual immunoglobulin dose to prevent breakthrough infections. Data from patients with X-linked agammaglobulinemia (XLA) were analyzed for comparison.

METHODS

Inclusion criteria

Patients that met the CVID criteria[30] were selected, namely those with a reduced serum IgG level (<6.0 g/L) and either a serum IgA level <0.8 g/L or a serum IgM level <0.5 g/L or both, over 4 years of age at diagnosis, and exclusion of other conditions or therapies associated with antibody failure. Of these patients with CVIDs, 73 had serum IgG levels <3.5 g/L at diagnosis, and therefore, specific antibody testing was not essential for the diagnosis.[29] Of the remaining 17 patients, 12 had evidence of absent specific responses, and 5 were diagnosed elsewhere. Male patients with a CVID and no detectable circulating B cells had normal Bruton tyrosine kinase but were not tested for rare autosomal recessive defects in B-cell development because all these patients presented over the age of 4 years and such conditions present in early childhood. Patients were excluded if there was less than 12 months of data or noncompliance with therapy or monitoring. Data from patients with XLA was collected for comparison by using the same exclusion criteria. XLA was defined as pan-hypogammaglobulinemia, no detectable circulating B cells, exclusion of thymoma or B-depleting therapies in adults, and the presence of a mutation in Bruton tyrosine kinase.[30]

Data extraction

The Oxford PID Database (FileMaker Pro version 6, Filemaker Inc, UK) was set up in 1987 to collect demographic and infection data alongside details of therapies. Data on infections (including infection site, pathogen type, and treatment details), administration route of immunoglobulin, dose in grams per kilogram per month, and clinical complications were entered prospectively from the patient notes at the start of immunoglobulin therapy or on referral to Oxford for patients diagnosed previously. A separate Excel spreadsheet (Microsoft Corp, UK) was kept for laboratory data including preinfusion (trough) serum IgG, IgA, and IgM levels; liver function tests; blood counts; C-reactive protein; and β2-microglobulin levels. Immunoglobulin levels and liver function tests were measured routinely every 6 to 12 weeks as part of safety monitoring.

Validation of the data was carried out by verification from the patient notes, treatment logs (patients on home therapy documented infections on their infusion logs), and patients' monthly symptom diaries in the event of a discrepancy. Time on intramuscular immunoglobulin was not included in the analysis because it has been shown by others to be inadequate in terms of infection control; these data were used in the decade analyses only.

Data analysis

Graphs of IgG, IgA, and IgM levels were plotted against time for each patient. Commencement of replacement therapy and dose changes were highlighted on each graph. The entry point for each patient into the analysis was the point at which the serum IgG level was stable; stability was defined as ≤1.5 g/L variation from the mean trough IgG over at least 4 months.

To allow for seasonal variation in infections (see Results), the mean trough IgG levels for each 12-month period after stabilization were calculated. Periods were restarted if there was a change in dose or if there was a persistent change in the trough IgG level (≥1.5 g/L variation from the mean). Individual periods relating to a given patient were excluded if: there were incomplete infection data or infrequent measurements of IgG (<3 per year); or there was a period of noncompliance with infusions; or IgG trough levels were variable because of another clinical condition such as ascites, renal loss, or transient severe diarrhea (such as in giardiasis); or the patient stopped receiving immunoglobulin therapy for a trial period. In total, 885 periods were created covering 741 patient-years; of these, 485 (55%) were a full 12 months, 400 periods (45%) were <12 or >12 months in duration. Of these 400 periods, 1538 months covered the winter period (October to March), and 1541 months were in the summer (April to Sept).

The dose of immunoglobulin replacement was calculated in grams per kilogram per month. For children, the mean weight was calculated for each period. For adults, a change in weight was used only if there was a persistent change >10 kg.

Confirmation of bacterial infection was sought using radiologic/laboratory/microbiological findings and responses to antibiotics. Infectious episodes were scored as minor (infection score 1) if not treated or by topical antibiotics only; moderate (infection score 2) if treated with oral antibiotics/antifungals/antivirals or if documented bacterial conjunctivitis; and severe (infection score 3) if treated with intravenous antibiotics/antifungals/antivirals. Minor infections were not analyzed because of a lack of reliable data. Only acute infections were included; recurrence of the same clinical features within 7 days was considered to be a continuation of the original infection.

Complications and clinical phenotypes

The common complications of bronchiectasis (as assessed by computerized tomography) and splenomegaly (as assessed clinically or by ultrasound) were recorded but not included for clinical phenotyping. Clinical phenotypes were based on the original clinical phenotyping criteria.[3] These have recently been revised in that autoimmunity has been split into cytopenias and organ specific autoimmunity as separate phenotypes because the prognoses were different. In addition, unexplained hepatomegaly has been excluded from the polyclonal lymphoproliferation phenotype because of uncertainty about the etiology of an enlarged liver.[31] These revised criteria were used in this study. If a disease-related complication defining a particular phenotype developed during the follow-up period (detected with careful monitoring at clinical follow-up with blood counts for cytopenias, regular computed tomography scans for bronchiectasis and serum immunoglobulins with β2-microglobulin levels and biopsies for lymphoproliferation), the periods were divided by presence or absence of the phenotype.

Statistics

Where data were amalgamated over each patient observation period, to determine a single statistic (eg, infection rate), basic univariate statistical approaches were used (χ^2 tests for binomial/multinomial data, Wilcoxon rank-sum tests for quantitative outcomes, and z tests for comparison of rates on the basis of an assumed underlying Poisson distribution). Because several periods from single patients were included, such analysis was controlled for each subject.

For time-dependent patient data, analyses needed to account for the potential correlative structure of multiple observations per subject. Linear

TABLE I. Patient characteristics for 90 patients with a CVID and 15 patients with XLA

Characteristics	CVIDs	XLA
Data analyzed (mo)	8891	1152
Patient-years covered	740.9	96
Percentage of patients with follow up of ≥5 y	66	60
Mean age at start of analysis (y) (median, range)	41 (39, 4-74)	17 (15, 2-39)
Mean age at end of analysis (y) (median, range)	49 (50, 8-85)	24 (21, 9-53)
Patients receiving only SCIg	6	0
Patients receiving only IVIg	59	13
Patients receiving both IVIg and SCIg	25	2

IVIg, Intravenous immunoglobulin; *SCIg,* subcutaneous immunoglobulin.

mixed modeling[32] was used with each patient as a random effect in the model. Partial squared correlation coefficients (pR^2) were determined by modified least-squares algorithms and were computed to determine the contribution of an individual predictor to the specific outcome variable. The comparison of regression coefficients between different models was evaluated by using an approximate *t* test based on the difference of the coefficients divided by the square root of the sum of the individual SEs of the coefficients. Statistical significance was declared with a *P* value less than .05.

RESULTS

Patient characteristics

One hundred and fifteen patients with confirmed CVIDs and 17 with XLA, seen regularly in the past 25 years (1982-2007), were included initially. Of these, 25 patients with CVIDs were excluded, 10 for noncompliance with therapy, poor infection history or missing serum IgG data, and 15 with less than 1 year available since stabilization of trough IgG. Two patients with XLA were excluded, 1 for noncompliance and 1 for <1 year of follow-up. Patient characteristics are shown in Table I. Diagnostic IgG levels, available in 85 patients out of the total 115 CVIDs patients studied, ranged from <0.1 to 5.4 g/L.

To determine the role of prophylactic antibiotics on infection rates, data from 18 patients with CVIDs who received prophylactic antibiotics for respiratory infections for ≥3 months were analyzed. Only 3 of 18 patients showed reduced numbers of infections (reduction of >4 in the annual infection score), and these were excluded from the infection analysis. Overall, 10 patients received antibiotics for nonrespiratory indications (after splenectomy, n = 4; transiently with immunosuppressant therapy, n = 1; or as prophylaxis for gut, skin, or urinary tract infections only, n = 5), so the data from these periods were included in the infection analysis. Three of the 18 patients had serious breakthrough infections while on prophylactic antibiotics for respiratory infections. Eight patients with XLA had received antibiotic prophylaxis, but only 1 had a reduction in the infection score; he was also excluded from the infection analysis.

Infection outcomes

Therapeutic immunoglobulin doses were adjusted in accordance with infection data rather than to achieve a particular trough IgG level. The overall bacterial infection frequency was low (2.16 infections per patient-year) and the incidence of serious infection particularly so. The mean bacterial infection score per patient-year was 4.7 (median, 4; range, 0-32).

The sites of infections are shown in Fig 1 and this article's Table E1 in the Online Repository at www.jacionline.org. To assess seasonal variation, the total number of respiratory infections over 741 patient-years was calculated for each month. Analysis showed that there were increased numbers of both lower respiratory tract infections ($P = .02$) and upper respiratory tract infections ($P = .04$) in winter (4444 winter and 4447 summer months were analyzed).

There were 1530 total infections (moderate and severe; Fig 1; Table E1), of which 9 were viral and 5 were fungal. Of the 9 viral infections, 7 were episodes of shingles in: patients on corticosteroids, recipients of recent chemotherapy, or elderly patients. Only 1 fungal infection was severe, and 4 were non-invasive moderate infections. There were 1516 bacterial infections, of which only 25 (1.7%) were treated with intravenous antibiotics and therefore classified as serious. These 1516 bacterial infections formed the basis of the remaining analysis; the vast majority (86%) were respiratory.

In any period, the mean trough IgG level correlated strongly with the replacement dose of immunoglobulin (pR^2, 0.33; $P < .0001$). There was a weak relationship between infection score per patient-period and mean trough IgG (pR^2, 0.007; $P = .02$), although not with the immunoglobulin replacement dose at that time.

Efficacy of immunoglobulin replacement therapy

Decade analysis. The data covered almost 3 decades, from 1980 to 2007. There was a significantly higher mean trough IgG in the 2000s (10.06 ± 2.46 g/L) compared with the 1980s (6.44 ± 2.02 g/L) and the 1990s (8.28 ± 2.35 g/L; $P \leq .000001$; see this article's Fig E1, *A,* in the Online Repository at www.jacionline.org). This was accompanied by a significant increase in the mean doses of replacement therapy, from 0.51 ± 0.18 g/kg/mo in the 1980s to 0.58 ± 0.28 in the 1990s and 0.57 ± 0.24 in the 2000s ($P = .02$; Fig E1, *B*). However, despite a decrease in mean infections rates from the first (2.8 ± 3.0 infections per patient-year) to the second decade (1.9 ± 1.9), infection rates remained fairly constant in the third decade (2.3 ± 2.0) though a higher proportion of patients had no infections in the third decade (Fig E1, *C*).

Trough IgG levels and immunoglobulin doses to prevent breakthrough bacterial infections. To determine the trough IgG levels and immunoglobulin replacement doses to prevent breakthrough bacterial infections, a definition of *infection-free* was determined. Three different thresholds of infection were used: less than or equal to an annual infection score of 4.5, less than or equal to an annual infection score of 2.5, and an annual infection score of 0. The mean doses and trough IgG levels per patient were calculated for those periods relevant to these infection thresholds.

There was a wide range of trough IgG levels in periods in which breakthrough infections were prevented (infection-free); these were similar at each level of definition of infection prevention (Fig 2, *A-C*; see this article's Table E2 in the Online Repository at www.jacionline.org). Patients with XLA also displayed a large range of IgG levels to maintain an infection-free state (8-13 g/L in all 3 infection thresholds). Trough IgG levels to prevent all infections were significantly higher in patients with XLA compared

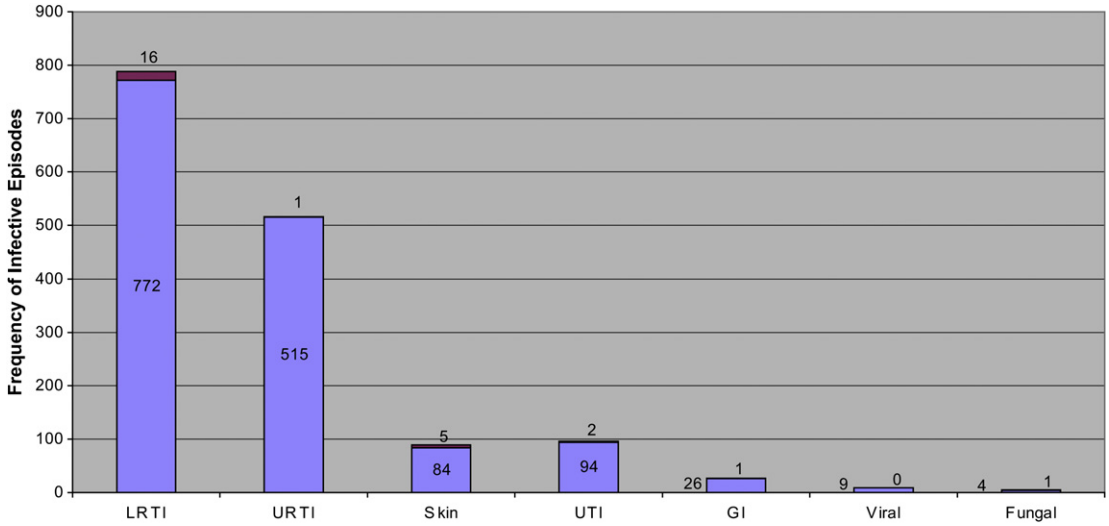

FIG 1. Number, type, and severity of infections in patients with CVIDs over the 8891 months of analyzed data. *Red bars* are the proportion of each infection type that was classified as severe. *GI*, Gastrointestinal infection; *LRTI*, lower respiratory tract infection; *URTI*, upper respiratory tract infection; *UTI*, urinary tract infection.

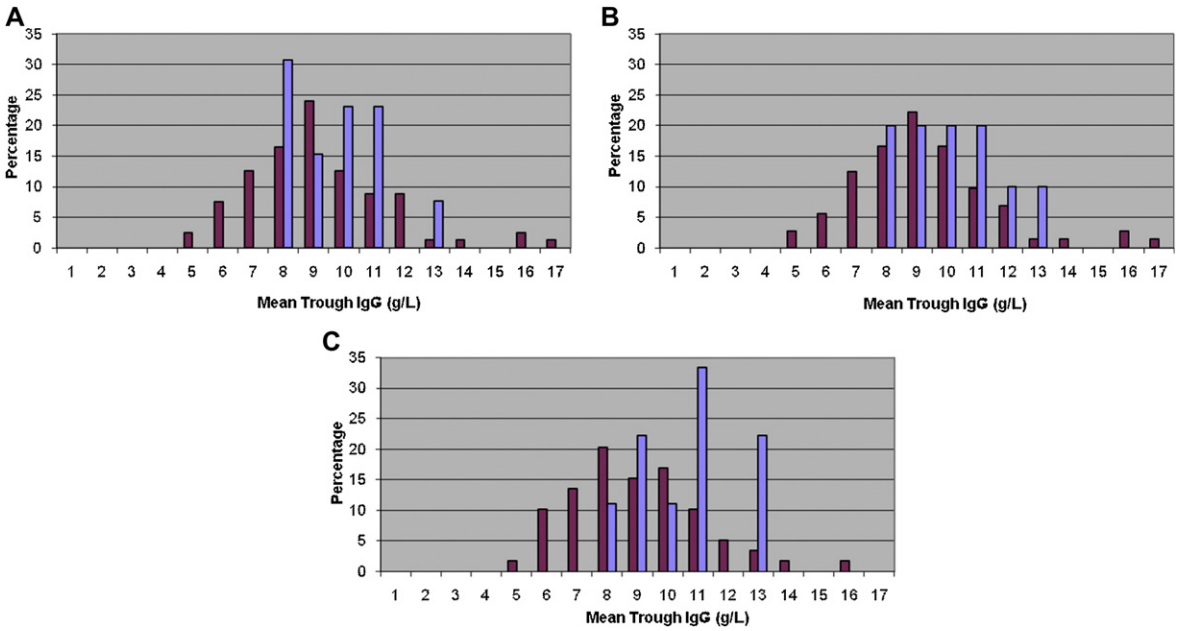

FIG 2. Mean trough IgG levels to keep individual patients infection- free. Mean IgG trough levels are shown relative to the total number of patients with CVIDs or XLA. *Red bars* represent patients with CVIDs; *blue bars* represent patients with XLA. **A,** Periods using a threshold of infection score at ≤4.5 per year. **B,** Periods using a threshold of infection score at ≤2.5 per year. **C,** Periods using a threshold of infection score at 0 per year.

with patients with CVIDs ($P = .03$). There was also a large variation in replacement doses of immunoglobulin required to prevent breakthrough infections in individual patients, ranging from 0.2 to 1.2 g/kg/mo for all infection thresholds (Table E2). Patients with XLA required significantly higher replacement doses to prevent all infections compared with patients with CVIDs ($P = .01$; Table E2).

The increases from baseline levels of serum IgG and the IgG level to keep patients infection free (infection threshold of ≤4.5 infection score per year) in a given period were then examined in 71 of these patients for whom baseline IgG and complete infection data were available. Correlations were sought between the final level of IgG resulting in absence of infection and dose of immunoglobulin used to achieve this in relation to the baseline (starting) IgG level at diagnosis. For those patients with baseline IgG levels <1 g/L (mean, 0.4; n = 32), doses varied from 0.4 to 1.2 g/kg/mo (mean, 0.61); for those with levels between 1 and 3.5 g/L (mean, 2.0; n = 27), doses ranged from 0.2 to 1.2 g/kg/mo (mean, 0.5); and those ≥3.5 g/L (mean, 4.2; n = 12) were 0.3 to 0.7 g/kg/mo (mean, 0.5). Mean trough IgG levels were similar: 9.13 g/L for the first group, 9.35 g/L for the second group, and 9.6 g/L for those with the highest baseline IgG levels.

There was a strong correlation between serum IgG levels at baseline (starting) and the increases to the IgG levels at which

TABLE II. Comparison of the effect of clinical phenotype on replacement doses of immunoglobulin in patients with a CVID

	Patient clinical status	No. of patients in each category	Mean replacement dose of immunoglobulin	*P* value comparing mean dose with and without phenotype/complication
(a)	No complications	32	0.47 ± 0.16	$<10^{-6}$
	Disease-related complications	58	0.67 ± 0.26	
(b)	Clinical phenotype			
	Enteropathy	9	0.88 ± 0.31	$<10^{-6}$
	No enteropathy	81	0.54 ± 0.21	
	Cytopenias	24	0.70 ± 0.30	.001
	No cytopenias	66	0.55 ± 0.22	
	Lymphoproliferation	23	0.70 ± 0.26	.003
	No lymphoproliferation	67	0.55 ± 0.24	
	Organ-specific autoimmunity	31	0.65 ± 0.22	.07
	No organ-specific autoimmunity	59	0.56 ± 0.25	
	Malignancy	5	0.85 ± 0.20	.03
	No malignancy	85	0.58 ± 0.24	
(c)	Individual			
	Granuloma	15	0.62 ± 0.22	.51
	No granuloma	75	0.58 ± 0.25	
	Lymphoid interstitial pneumonitis	13	0.72 ± 0.23	.02
	No lymphoid interstitial pneumonitis	77	0.57 ± 0.24	
	Lymphadenopathy	7	0.71 ± 0.29	.08
	No lymphadenopathy	83	0.57 ± 0.24	

Each of the 6 clinical phenotypes are assessed, in addition to the complications that make up the phenotype polyclonal lymphoproliferation. (a) All phenotypes; (b) individual phenotypes; (c) individual complications.

patients were infection-free (infection threshold of ≤4.5 infection score per year; Spearman rank correlation = –0.58; $P \leq .000001$).

Role of complications. The patients with bronchiectasis received higher doses of immunoglobulin (mean, 0.70 ± 0.29 g/kg/mo compared with 0.53 ± 0.20 g/kg/mo without bronchiectasis [$P = .006$]), although the mean baseline (starting) values for serum IgG were similar: 1.8 g/L for those without bronchiectasis and 1.39 g/L for those with bronchiectasis ($P = .11$). The infection scores per patient-period in the presence or absence of bronchiectasis did not differ significantly, and mean trough IgG levels were also similar (9.2 ± 2.4 g/L with bronchiectasis compared with 8.9 ± 2.6 g/L without). When the threshold of ≤4.5 bacterial infections per year was used to define infection-free, 36 of 41 (88%) of the patients with bronchiectasis were infection-free; when the infection threshold of ≤2.5 infection was used, 83% of patients remained infection-free.

To explain why higher doses of therapeutic immunoglobulin resulted in similar IgG trough levels in patients with and without bronchiectasis, the correlation between serum IgG concentration and the dose of replacement immunoglobulin was examined. This resulted in 885 patient-periods being evaluated (over 741 patient-years), 288 in those with bronchiectasis and 597 in those without. The regression coefficient for trough IgG levels against replacement doses of immunoglobulin for patients with bronchiectasis was 0.41—that is, for every 0.1 g/kg/mo increase in replacement dose of immunoglobulin, the trough IgG increased by 0.41 g/L. In the absence of bronchiectasis, the regression coefficient was higher at 0.82 ($P \leq 10^{-6}$; see this article's Fig E2 in the Online Repository at www.jacionline.org).

The relevance of splenomegaly was examined. Although there was a difference between the replacement dose of immunoglobulin given in the presence or absence of splenomegaly (0.70 ± 0.29 g/kg/mo and 0.55 ± 0.23 g/kg/mo, respectively; $P < .000001$), mean trough IgG levels were not significantly different (8.7 ± 2.7 g/L and 9.1 ± 2.5 g/L in the presence or absence of splenomegaly; $P = .11$). There was no significant difference in the mean baseline (starting) values for serum IgG: 1.57 g/L for those without splenomegaly and 1.69 g/L for the patients with splenomegaly ($P = .69$). Regression coefficients for trough IgG levels against replacement doses of immunoglobulin with or without splenomegaly were similar (0.73 with splenomegaly and 0.68 without). There was no significant difference between infection scores in the presence or absence of splenomegaly.

Role of clinical phenotypes. A search was made for associations between CVID clinical phenotypes and replacement doses of immunoglobulin, trough IgG levels, or infection rates. The presence of any disease-related phenotype resulted in the administration of a higher dose of replacement therapy compared with patients with no disease-related complications (Table II). Patients with enteropathy, cytopenias, and polyclonal lymphoproliferation were treated with significantly higher doses of immunoglobulin replacement therapy to prevent infections. Those with a lymphoid malignancy also received a higher replacement dose of immunoglobulin, although this did not reach significance because of low numbers. The presence of organ-specific autoimmunity made no significant difference to the dose of replacement therapy. Within the individual complications that comprise the polyclonal lymphoproliferative phenotype in CVIDs, only those patients with lymphoid interstitial pneumonitis (LIP) received significantly higher doses of replacement therapy ($P = .02$).

In relation to infection scores, patients without any disease-related complications had significantly lower infection scores (mean, 4.1 infection score per patient-period) compared with those with a disease-related phenotype (mean, 5.1 infection score per patient-period; $P = .002$). Infection scores were significantly higher in patients with polyclonal lymphoproliferation ($P = .01$) or organ-specific autoimmunity (OSAI) ($P = .02$). There were no significant differences in infection scores between patients with or without cytopenias, enteropathy, or malignancy. Within the polyclonal lymphoproliferation phenotype, only those with LIP had a higher mean infection score of 6.3 compared with 4.4 without ($P = .003$).

DISCUSSION

This is the first study to determine the relationships between doses of replacement therapy, infection rates, and trough IgG levels and to compare these for patients with different clinical CVIDs phenotypes or common complications. Furthermore, this is a substantial group of patients with CVIDs followed over 741 patient-years in 1 center using validated data over 22 years. The policy of adjusting the dose of replacement therapy to reduce the infection rate to a minimum in a given patient has generated a wide range of dose regimens for analysis. The frequent trough IgG measurements allowed correlations among stable serum IgG levels, immunoglobulin doses, and infection rates to be determined. To avoid obvious confounders, 2 potential influencing variables were considered first: seasonal variation and antibiotic prophylaxis. As expected, there were significant seasonal differences in both upper and lower respiratory infections, but the effect of prophylactic antibiotics was minimal in this cohort.

As expected in patients with CVIDs, only a very small proportion (0.9%) of the total number of infections were fungal or viral in origin. The only severe nonbacterial infection was a fungal (*Aspergillus*) chest infection in a patient who had received long-term corticosteroid therapy. This patient accounted for 3 of the total of 5 fungal infections. Analysis of bacterial infections showed that the majority of infections (86%) were respiratory, similar to reports of other cohorts of patients with CVIDs.[9,25]

Encouragingly, only 1.7% of the total bacterial infections were severe, in line with the local policy of adjusting the therapeutic immunoglobulin dose to minimize breakthrough infections. The low number of serious infections supports previous studies of partial efficacy showing reduced rates of pneumonia[4,8,10] and serious infections[5,9,13] after commencement of replacement therapy. Locally the mean trough IgG has significantly increased over the past 3 decades, highlighting the need to provide updated guidance.[9,16-21,23-25] Although the mean replacement dose of immunoglobulin increased over the 3 decades, the mean numbers of infections per patient-year appears to have reached a plateau, hence the need to break the data into infection-free periods for each patient.

This study provides evidence to support the clinical view that the trough IgG and dose of replacement therapy to maintain a minimal infectious burden is unique to the individual. Recently Bonagura et al[15] provided data in 2 illustrative patients, suggesting that each patient requires an individualized dosing regimen for maximum health benefit. However, no large study has attempted to test the hypothesis. The wide range of mean trough IgG levels per patient to achieve an annual infection score of less than or equal to 4.5 or 2.5 or to prevent all infections completely reflects the wide range of IgG levels in healthy individuals. Although 3 different thresholds of breakthrough infections were used, these gave similar results, and hence, an infection score of 4.5 (equivalent to 2 moderate bacterial infections per year) seems reasonable as a definition of infection prevention. Protective trough IgG levels were achieved with a large range of replacement doses (0.2-1.2 g/kg/mo), supporting individualization of dose of in terms of infection prevention, as was also found in patients with XLA.

The strong inverse correlation between serum IgG levels at baseline and the increases to protective IgG levels support the view that IgG catabolism increases with higher baseline IgG levels.

Patients with bronchiectasis require twice as much replacement therapy to achieve the same IgG level compared with those free of bronchiectasis. de Gracia et al[5] reported similar results in patients with a CVID and chronic pulmonary disease. Whether this is a result of increased catabolism or loss remains unanswered. Our data also demonstrated that the infection scores were no different between those with and without bronchiectasis, indicating that the increased doses of immunoglobulin were sufficient to prevent an excess of infections regardless of structural damage.

It is of interest that the presence of the common complication of splenomegaly resulted in higher doses of immunoglobulin but achieved similar trough IgG levels as well as similar infection rates. The regression coefficients in these patients compared well with those without splenomegaly, despite these patients receiving higher doses of replacement therapy. This suggests that splenomegaly may not necessarily reflect lymphocyte activation and therefore higher IgG turnover but simply the increase in the vascular pool.

The effects of individual clinical phenotypes were also examined. Patients without disease-related complications received significantly lower doses of replacement therapy (compared with patients with other phenotypes) and had significantly lower infection scores. Those with LIP, cytopenias, and enteropathy received higher doses of replacement therapy. Only those with LIP had higher infection scores, although this is not surprising because patients with LIP are more susceptible to respiratory infections as a result of inflammation (or eventual fibrosis) and the use of corticosteroid therapy.

Our clinical practice follows the recent United Kingdom guidelines[29] and others.[26-28] Initial doses of 0.4 g/kg/mo IgG are used for patients without chronic lung disease and 0.6 g/kg/mo for those with bronchiectasis. Doses are adjusted in line with breakthrough infections. Because we have not seen serious breakthrough infections, a rate of 3 moderate bacterial infections per year justifies an increase in immunoglobulin dosage of around 0.15 g/kg/mo, usually given as weekly subcutaneous immunoglobulin or intravenous immunoglobulin every 2 weeks.

These data show, for the first time, that the doses of replacement immunoglobulin required to keep a particular patient free of bacterial infections are individual to that patient. The range reflects not only the wide diversity in healthy individuals but also the heterogeneity of patients with CVIDs, particularly the various clinical phenotypes. The limited data from patients with XLA support this view and suggest that this will apply to replacement therapy in all forms of primary antibody deficiency.

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Clinical implications: The goal of immunoglobulin replacement therapy in patients with primary antibody deficiencies should be to reduce breakthrough infections rather than to achieve a particular IgG trough level.

REFERENCES

1. Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, et al. International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007;120:776-94.
2. Wood P. Primary antibody deficiency syndromes. Ann Clin Biochem 2009;46: 99-108.
3. Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. Blood 2008;112:277-86.
4. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 2002;109:1001-4.
5. de Gracia J, Vendrell M, Alvarez A, Pallisa E, Rodrigo MJ, de la Rosa D, et al. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. Int Immunopharmacol 2004;4:745-53.
6. Skull S, Kemp A. Treatment of hypogammaglobulinaemia with IVIg 1973-1993. Arch Dis Child 1996;74:527-30.
7. De Santis W, Esposito A, Conti V, Fantauzzi A, Guerra A, Mezzaroma I, et al. [Health care and infective aspects in patients affected by common variable immunodeficiency assisted in the Lazio Regional Authority Reference Centre for Primary Immunodeficiencies]. Infez Med 2006;14:13-23.
8. Pourpak Z, Aghamohammadi A, Sedighipour L, Farhoudi A, Movahedi M, Gharagozlou M, et al. Effect of regular intravenous immunoglobulin therapy on prevention of pneumonia in patients with common variable immunodeficiency. J Microbiol Immunol Infect 2006;39:114-20.
9. Favre O, Leimgruber A, Nicole A, Spertini F. Intravenous immunoglobulin replacement prevents severe and lower respiratory tract infections, but not upper respiratory tract and non-respiratory infections in common variable immune deficiency. Allergy 2005;60:385-90.
10. Martinez Garcia MA, de Rojas MD, Nauffal Manzur MD, Munoz Pamplona MP, Compte Torrero L, Macian V, et al. Respiratory disorders in common variable immunodeficiency. Respir Med 2001;95:191-5.
11. Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007;27:308-16.
12. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999;92:34-48.
13. Bayrakci B, Ersoy F, Sanal O, Kilic S, Metin A, Tezcan I. The efficacy of immunoglobulin replacement therapy in the long-term follow-up of the B-cell deficiencies (XLA, HIM, CVID). Turk J Pediatr 2005;47:239-46.
14. Leen CL, Yap PL, McClelland DB. Increase of serum immunoglobulin level into the normal range in primary hypogammaglobulinaemia by dosage individualization of intravenous immunoglobulin. Vox Sang 1986;51:278-86.
15. Bonagura VR, Marchlewski R, Cox A, Rosenthal DW. Biologic IgG level in primary immunodeficiency disease: the IgG level that protects against recurrent infection. J Allergy Clin Immunol 2008;122:210-2.
16. Montanaro A, Pirofsky B. Prolonged interval high-dose intravenous immunoglobulin in patients with primary immunodeficiency states. Am J Med 1984;76:67-72.
17. Pirofsky B. Intravenous immune globulin therapy in hypogammaglobulinemia: a review. Am J Med 1984;76:53-60.
18. Bernatowska E, Madalinski K, Janowicz W, Weremowicz R, Gutkowski P, Wolf HM, et al. Results of a prospective controlled two-dose crossover study with intravenous immunoglobulin and comparison (retrospective) with plasma treatment. Clin Immunol Immunopathol 1987;43:153-62.
19. Eijkhout HW, Van Der-Meer JW, Kallenberg CG, Weening RS, van Dissel JT, Sanders LA, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia: a randomized, double-blind, multicenter crossover trial. Ann Intern Med 2001;135:165-74.
20. Roifman CM, Schroeder H, Berger M, Sorensen R, Ballow M, Buckley RH, et al. Comparison of the efficacy of IGIV-C, 10% (caprylate/chromatography) and IGIV-SD, 10% as replacement therapy in primary immune deficiency: a randomized double-blind trial. Int Immunopharmacol 2003;3:1325-33.
21. Roifman C, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. Lancet 1987;1:1075-7.
22. Pruzanski W, Sussman G, Dorian W, Van T, Ibanez D, Redelmeier D. Relationship of the dose of IVIg to the prevention of infections in adults with CVIDs. Inflammation 1996;20:353-9.
23. Sorensen RU, Polmar SH. Efficacy and safety of high-dose intravenous immune globulin therapy for antibody deficiency syndromes. Am J Med 1984;76:83-90.
24. Ochs HD, Fischer SH, Wedgwood RJ, Wara DW, Cowan MJ, Ammann AJ, et al. Comparison of high-dose and low-dose intravenous immunoglobulin therapy in patients with primary immunodeficiency diseases. Am J Med 1984;76:78-82.
25. Pettit SJ, Bourne H, Spickett GP. Survey of infection in patients receiving antibody replacement treatment for immune deficiency. J Clin Pathol 2002;55:577-80.
26. Tang M. Consensus recommendations for the use of immunoglobulin replacement therapy in immune deficiency. 1st ed, November 2008. Available at: http://www.apiieg.org/STATEMENTS.ASP. Accessed June 29, 2009.
27. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117:S525-53.
28. Shehata N, Hume H, Palda V, Anderson D, Bowen T, Warrington R, et al. Immune globulin for patients with primary immune deficiency: an evidence based practice guideline. Tranfus Med Rev 2010;24(suppl 1):S7-27.
29. Chapel HM, for the Consensus Panel for the Diagnosis and Management of Primary Antibody Deficiencies. Consensus on diagnosis and management of primary antibody deficiencies. Br Med J 1994;308:581-5.
30. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999;93: 190-7.
31. Ward C, Lucas M, Piris J, Collier J, Chapel H. Abnormal liver function in common variable immunodeficiency disorders due to nodular regenerative hyperplasia. Clin Exp Immunol 2008;153:331-7.
32. ED Mixed Models—theory and applications. Hoboken (NJ): John Wiley and Sons; 2004.

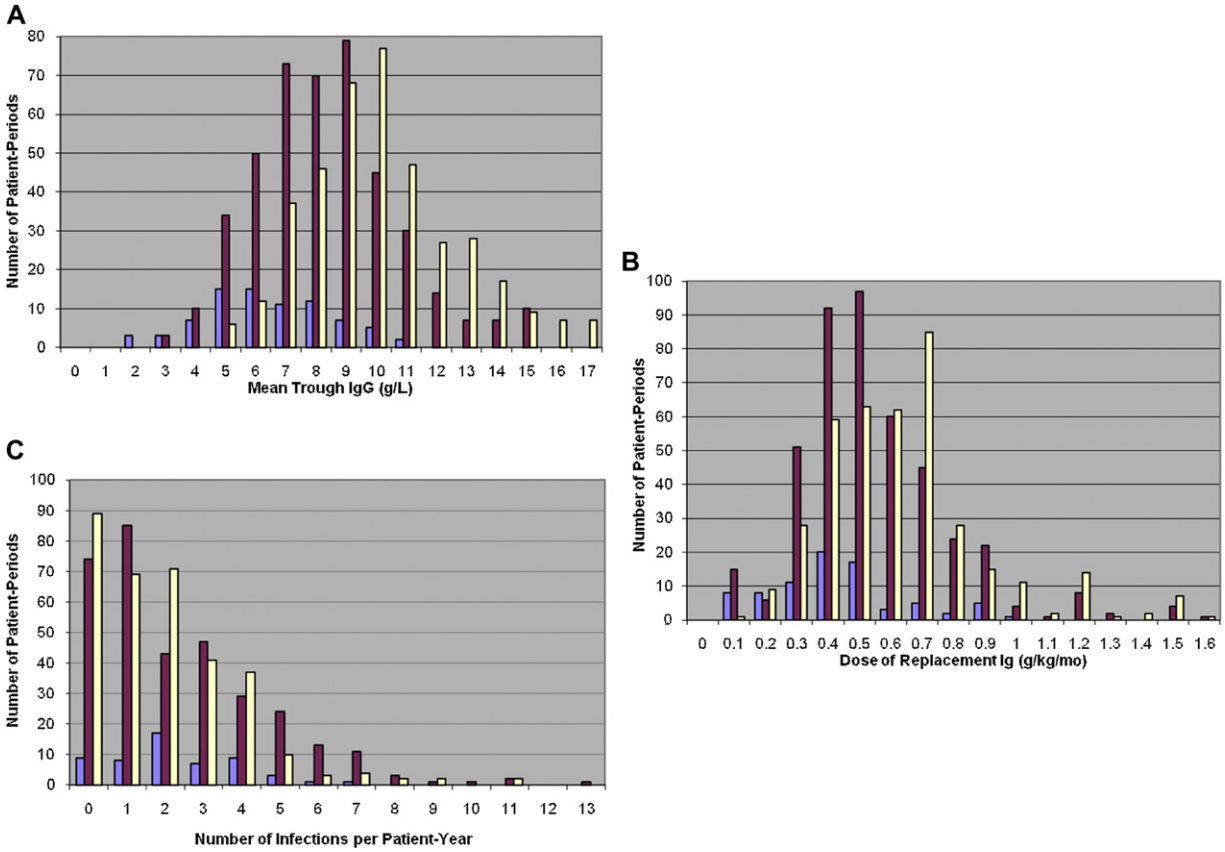

FIG E1. Distribution of mean trough IgG levels **(A)**, mean replacement dose of immunoglobulin **(B)**, and mean infection number per patient-year **(C)** for each patient-period across 3 decades. *Blue bars,* 1980 to 1989; *red bars,* 1990 to 1999; *yellow bars,* 2000 to 2007. Each bar represents the number of specific periods in that decade.

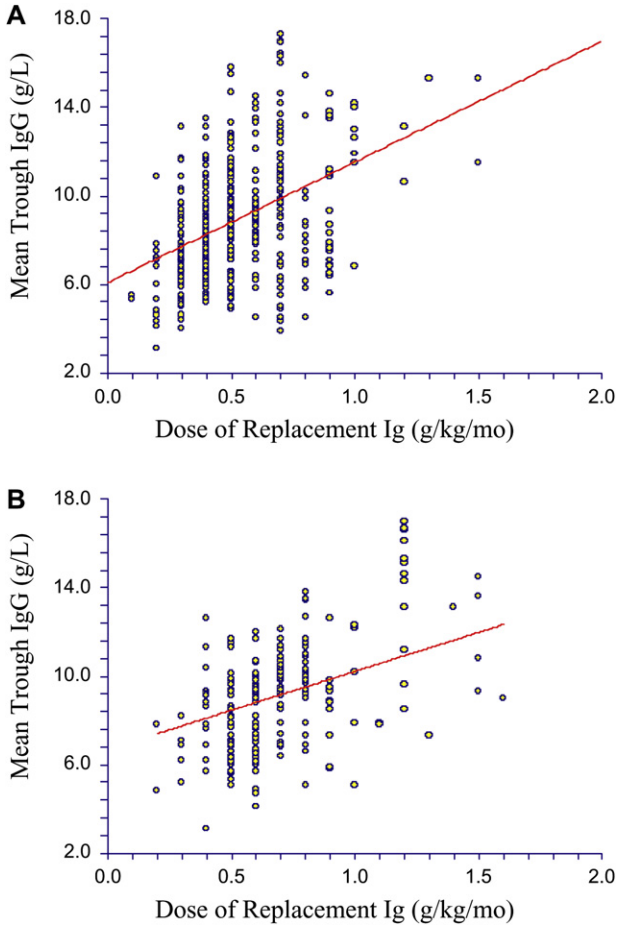

FIG E2. Correlation between trough serum IgG level and replacement immunoglobulin dose in patients without **(A)** and with **(B)** bronchiectasis for each given period of stable serum IgG concentration during follow-up. *Red line* represents the regression coefficient for that data set.

TABLE E1. Number, type, and severity of infections as experienced in patients with a CVID over the 8891 months of analyzed data

Infection site	Percentage of total infections (n = 1516)	Total	No. that were severe (% at that site)
Lower respiratory tract	52	788	16 (2%)
Upper respiratory tract	34	516	1 (2%)
Skin	6	89	5 (5.6%)
Urinary tract	6	96	2 (2%)
Gastrointestinal tract	2	27	1 (4%)
Total	100	1516	25 (1.7%)

TABLE E2. Comparison of mean trough IgG and replacement dose of immunoglobulin per patient to maintain breakthrough bacterial infections at a minimum in patients with a CVID and XLA

	Annual infection score	Mean trough IgG	Range	*P* value comparing CVIDs with XLA for mean trough IgG	Mean dose of replacement immunoglobulin	Range	*P* value comparing CVIDs with XLA for mean dose of replacement immunoglobulin	No. of patients
CVIDs	0	9.0 ± 2.2	5-16	.03	0.53 ± 0.19	0.2-1.2	.01	59
XLA	0	10.5 ± 1.6	8-13		0.67 ± 0.12	0.5-0.9		9
CVIDs	≤2.5	9.3 ± 2.4	5-17	.09	0.55 ± 0.19	0.2-1.2	.05	72
XLA	≤2.5	10.2 ± 1.5	8-13		0.64 ± 0.10	0.5-0.8		10
CVIDs	≤4.5	9.2 ± 2.3	5-17	.31	0.56 ± 0.18	0.2-1.2	.07	79
XLA	≤4.5	9.7 ± 1.5	8-13		0.63 ± 0.11	0.5-0.8		13

Three levels of infection thresholds were analyzed: annual infection score of ≤4.5, annual infection score of ≤2.5, and annual infection score of 0.